Interview Article

Interview: Dr. Muin J. Khoury Discusses the Future of Public Health Genomics and why it Matters for Personalized Medicine and Global Health

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Abstract: Muin J. Khoury, MD, PhD is the first and current director of the Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC) in the United States. The Office was formed in 1997 to assess the impact of advances in human genetics and the Human Genome Project on public health and disease prevention. As an internationally recognized institution, CDC's mission is to protect the health and safety of people, to provide credible information to enhance health decisions, and to promote health through strong national and international partnerships. For more than a decade, the CDC's Office of Public Health Genomics played an important role in development of a new hybrid field of investigation, 'public health genomics'. In the September 2009 issue of the Current Pharmacogenomics and Personalized Medicine (*CPPM*), Dr. Khoury shares his thoughts and immediate and long term vision on public health genomics, and why this new field of investigation is important for personalized medicine and global health. He is interviewed by a multidisciplinary team of researchers and educators: Abdallah S. Daar (McLaughlin-Rotman Centre for Global Health and School of Public Health Sciences, University of Toronto), Serge Dubé (Department of Surgery and Faculty of Medicine, University of Montreal) and Vural Ozdemir (Editor, *CPPM*, and Department of Social and Preventive Medicine, Faculty of Medicine, University of Montreal). Dr. Khoury received his BS degree in biology/chemistry from the American University of Beirut, Lebanon, and his medical degree and pediatric training from the same institution. He received a PhD in human genetics/genetic epidemiology and training in medical genetics from The Johns Hopkins University. Dr. Khoury is board-certified in medical genetics.

Key Words: Global public health, international development and policy, personalized medicine, preventive medicine, public health genomics.

INTERVIEW

Ozdemir

Thank you for agreeing to this interview, Dr. Khoury. You started work in the field of genetic epidemiology in the 1980s when the field was still in its infancy [1, 2]. You have then seen the shift in focus from genetics to genomics, and from rare monogenic diseases to study of complex polygenic and multifactorial traits such as common human diseases and host responses to drugs, nutrition and vaccines [3-14], with marked implications for global public health and international development policy [15-18]. More recently, your group played an active role in development of the field of public health genomics [19]. Could you briefly define the term 'public health genomics' for the *CPPM* readership? Do you (fore)see the public health theory and practice in a state of major transformation and gaining a new multidisciplinary identity with the incorporation of genomics?

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Khoury

Public health genomics is a multidisciplinary field concerned with the effective and responsible applications of genome-based knowledge and technologies to improve population health. This definition resulted from an international meeting held in Bellagio, Italy in 2005 [20]. As the name implies, the hybrid field is very much rooted in principles of public health. It takes a population perspective to the applications of new genome-based technologies to improve health. It focuses on prevention, evidence-based multidisciplinary science and ethical, legal and social implications, including addressing health disparities. Emerging genomic tools and technologies could have a significant impact on all areas of public health practice including infectious diseases, environmental and occupational health, and chronic diseases in addition to the more traditional genetic areas in maternal and child health (e.g., prenatal diagnosis, newborn screening and genetic services delivery). Public health has a multidisciplinary identity with the convergence of scientific population fields such as epidemiology, biostatistics, economics, behavioural and social sciences, ethics, legal and policy frameworks to address population health issues. The emergence of genomic tools and technologies will enhance the multidisciplinarity of public health and the development and

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applications of novel approaches to combat diseases of public health significance around the globe. In the United States, we have described the integration of genomics into public health essential functions (assessment, policy development and assurance) using the framework described by the Institute of Medicine [21]. We have also elaborated on the expansion of this framework to the 10 essential public health services [22]. Some variations of these public health functions and services are available in many parts of the world and can provide a useful framework for the intersection of genomics and public health. We have also described how genomics can address the growing schism between public health and medicine by focusing on prevention and early intervention from a population-based evidentiary perspective [23].

Ozdemir

Are the advances made in public health genomics also significant for pharmacogenomics and personalized medicine? If yes, what are some of the concrete promises and challenges?

Khoury

Advances in genomics will have an important long term impact on the development and utilization of drugs for treatment and prevention. The field of pharmacogenomics is promising a new era of personalized interventions based on the person's genotype, disease subtypes and characteristics and other forms of personalization. Such a field promises the delivery of the right drug to the right person at the right dose and at the right time, in order to maximize effectiveness and minimize side effects. Already we have a few examples of such applications in practice such as HER2 testing for breast cancer treatment [24] and HLA testing for Abacavir in the management of HIV [25]. Nevertheless, while the promise is real, the field is mostly in its early development [26]. Pharmacogenomic applications have to be subjected to principles of evidence-based medicine and comparative effectiveness research [27] to evaluate the net benefits and harms of their use in practice. Public health genomics can play an important honest broker role in developing and disseminating an integrated knowledge base on the clinical validity and utility of pharmacogenomic applications, in assuring the implementation of evidence-based recommendations in practice, and in evaluating their impact on population health. Already, we are seeing the beginning of the public health genomics approach to pharmacogenomics through CDC's EGAPP initiative (the Evaluation of Genomic Applications in Practice and Prevention), an independent multidisciplinary process featuring an independent working group making evidence-based recommendations on pharmacogenomic and other genomic applications in practice in the United States [28]. As of July 2009, 5 evidence-based reviews and 4 recommendations have been made by the group [29].

Daar, Dubé and Ozdemir

You recently proposed four concrete steps (T1 to T4) for effective translation of basic genomics discoveries to "real world" health outcomes in practice [30]. Moreover, you estimated that no more than 3% of the published human genomics studies focus beyond discovery oriented applications [30]. Why is this significant? And what can be done to remedy this translational knowledge gap?

Khoury

Translation of new scientific discoveries into population health benefits often takes a long time with different lines of research at multiple steps (T1 to T4). Genomics is not alone in the constriction in the translation highway and the phenomenon of "lost in translation" which we have been seeing repeatedly in other areas of medicine and public health [31, 32]. In the United States, there is big emphasis on genomics discovery research but much less on research that allows discoveries to be evaluated for integration into practice, and for documenting their health impact among all segments of the population. Such research includes but is not limited to epidemiologic investigations of gene-environment interactions, evaluation of clinical validity of genetic information, randomized clinical trials to measure benefits and harms, behavioural, communication and social science research to assess impact of genetic information. Even when we have good evidence for gene-based therapeutics or diagnostics, research on implementation, diffusion and dissemination is often not done, and adoption in practice is uneven, underresourced and not well distributed across all segments of the population. Right now, there may be a few genomic applications that are "lost in translation". However, currently a more prominent genomics translation challenge is "premature translation" where such applications are not ready to be integrated into practice. An example of premature or inappropriate translation is the availability of direct-to-consumers personal genome profiles [33]. What the translation article showed was that the main focus of genetic research is still on discovery. However, we need more research done to evaluate the emerging candidate applications and to build the evidence base for their appropriate utilization in practice. I hope that the public and private sectors will collaborate more in investing in the translation research infrastructure (such as clinical trials and population registries) to move genomics discoveries towards clinical and population health applications.

Daar

How will human genomic research benefit people in the developing world and how can governments invest intelligently in the developing world to derive maximum benefit from genomics research?

Khoury

Population-based genomic research has the potential to benefit health in both the developed and developing world. Of course, the distribution of disease burden is different in the developing world, with an important emphasis on combating infectious diseases, malnutrition and infant mortality. However, the emergence of chronic diseases such as diabetes and heart disease is also a global public health phenomenon. The discoveries made resulting from genomics including better or targeted interventions (such as vaccines or drugs) as well as diagnostic, screening or predictive tests could benefit global health. Nevertheless, in order to reap the health benefits of genome-based research, targeted investments will be

needed to develop the laboratory capacity to measure genomics in large scale populations, investments in biobanks and epidemiologic cohort studies to assess health outcomes, as well as training and education of the workforce and the general public. Investments in clinical studies and randomized clinical trials will be needed to evaluate the utility of these new applications. Importantly, investments in ethical and legal frameworks will be needed to facilitate translation research and protect individuals and communities from potential negative consequences of genetic testing. In addition to investments in human genomics, a larger focus on technology including gene-based technologies for pathogen discovery, plants and foods and renewable sources of energy could all have beneficial global health impact.

Dubé and Ozdemir

Genomics science transcends the conventional laboratory bench space [6] and includes a highly heterogeneous cast of stakeholders in society who have a plurality of interests that are often in conflict [12]. What are the necessary measures and policy interventions to ensure genomics innovations are driven by objective and balanced evidence from the laboratory to global society? From the standpoint of education, how can the emerging genomics knowledge be transferred to new generations of health care providers to ensure the effectiveness and safety of health care interventions (e.g., pharmacotherapy, nutrition, vaccines, medical devices, etc).

Khoury

I have recently written about the "evidence dilemma" in genomic medicine [34]. Without subscribing to genetic exceptionalism, we can see today that the leading edge of genomic technology is so far ahead of practical health applications that can improve health and prevent disease for individuals, families and communities. Some have labelled genomics as "disruptive technology" [35] with the potential of having profound shifts on clinical practice. Nevertheless, like in all emerging areas of science and technology, I think requiring evidence-based genomic applications in medicine is a necessity and will put the field on more stable footing on the long run and avoid the pitfalls of unwarranted, premature or potentially harmful applications. In order to succeed, the competing interests of different stakeholders have to be managed and reconciled in a collaborative framework that rewards both scientific innovations as well as appropriate clinical applications. On the short run, we need to develop a policy framework that requires accurate laboratory testing, and truth in advertising about potential health benefits, protection from untoward psychological or social effects, as well reimbursements of genetic services that can benefit individuals, families and populations. In the United States, a policy framework has been pursued by the Secretary's Advisory Committee on Genetics, Health and Society [SACGHS, 36]. SACGHS, an independent advisory group to the Department of Health and Human Services has provided several recommendations for implementing appropriate utilization of genetic services while facilitating population-based research (e.g., large cohort studies) and pharmacogenomic research [36]. In the meantime, I believe that health providers and consumers need to have the latest credible information at their fingertips in order to make rational health decisions in a rapidly moving field. We see that in the phenomenon of DTC genetic testing in the US and other parts of the world. Recently, a multidisciplinary panel convened by CDC and NIH strongly recommended that timely and accurate information should be provided to consumers and health care providers [37]. Calls for a mandated genetic test registry have been made by the SACGHS [38] and others [39]. The CDC recently launched a collaborative initiative, the genomic applications in practice and prevention network (GAPPNet) to facilitate knowledge synthesis and dissemination to stakeholders through an integrated online knowledge base [40]. Multifaceted education efforts are needed in genomics for multiple groups including providers, the general public, policy makers and researchers from different fields. This is an important public health function as the field matures towards more validated applications that could be used in clinical practice.

Ozdemir

In order to maximize the transparency, quality and completeness of reporting of genetic association findings, the *CPPM* encourages authors to consider the recent STREGA recommendations [41]. Can you share your thoughts on ways in which STREGA guidelines may contribute to development of evidence based genomics medicine?

Khoury

STREGA recommendations were the product of several years of work by collaborators from the Human Genome Epidemiology Network (HuGENet) [42] in partnership with the STROBE global movement (Strengthening the Reporting of Observational Epidemiology) [43]. HuGENet was launched by CDC in 1998 as a global collaboration of individuals and organizations interested in evaluating the impact of human genetic variation on population health and how this information can be used to improve health and prevent disease. HuGENet collaborators have advocated that the credibility of reported genetic associations depends heavily on the quality of primary research, the availability of published and unpublished observations, the avoidance of publication bias and other biases, as well as the synthesis and dissemination of findings through systematic reviews and meta-analyses. The STREGA guidelines were developed to enhance the reporting of genetic association studies. The reason why these guidelines are important is because they feed into the first of several evaluation steps in evidence-based genomic medicine. Namely, they help with the evaluation of the clinical validity of the genomic application (mainly genotype-phenotype correlations). Other important multifaceted evidence based evaluations of genomic applications include the analytic validity, clinical utility and the ethical, legal and social issues initially described under the ACCE framework [44] The ACCE framework was adopted and modified by the EGAPP working group. As described above, the working group has developed evidence based methods for evaluating genomic applications in clinical practice and disease prevention.

Dubé and Ozdemir

From the point of technology and its applications, the speed at which genomics has advanced is remarkable. The history over the past 20th century tells us, however, that the human populations do not always display a commensurate cognitive evolution to proactively discern and monitor the multiple impacts of technologies on society or the environment. To this end, what are your thoughts on the emerging practice of 21st century science and medicine? What are some realistic schemas under which population genomics variation can be effectively integrated with social determinants of health, and genome-environment interactions more generally?

Khoury

I subscribe to an ecologic model of disease [45] that posits that human diseases and disability is the product of complex gene-environment interactions that occur throughout the lifespan. I define the "environment" broadly to include infectious, chemical, physical, social and factors. Most of the targets for public health interventions will be on the environmental side. Even for classical genetic diseases such as phenylketonuria, public health interventions can be environmental (low phenylalanine diet) delivered after screening and early identification of affected individuals. Many have voiced concerns about the value of genomic research for prevention and public health, especially for complex diseases with risk factors that are amenable to environmental modification [46]. Given that gene-environment interactions underlie almost all human diseases, the public health significance of genomic research on common diseases with modifiable environmental risks is based not necessarily on finding new genetic ''causes'' but on improving existing approaches to identifying and modifying environmental risk factors to better prevent and treat disease [47]. Such applied genomic research for environmentally caused diseases is important, because it could help stratify disease risks (e.g., using genetic information including family history) and differentiate interventions for achieving population health benefits; it could help identify new environmental risk factors for disease or help confirm suspected environmental risk factors; and it could aid our understanding of disease occurrence in terms of transmission, natural history, severity, etiologic heterogeneity, and targets for intervention at the population level. While genomics is still in its infancy, opportunities exist for developing, testing, and applying the tools of genomics to clinical and public health research, especially for conditions with known or suspected environmental causes. This research is likely to lead to population-wide health promotion and disease prevention efforts, not only to interventions targeted according to genetic susceptibility.

Ozdemir and Dubé

We are increasingly seeing two parallel and potentially conflicting trends in medicine and modern scientific practice: (1) the need for technical hyperspecialization and (2) ability for integration of knowledge domains from diverse disciplines who do not often share similar standards, values and priorities. Do you have any thoughts on this dilemma and the need for truly multidisciplinary and hybrid identities that are well integrated across disciplines and 'ways of knowing'? It is interesting to note that the year 2009 coincides with the 200th anniversary of the birth of Charles Darwin (12 Feb 1809 – 19 April 1882) [48]. Nature has given us numerous examples of 'hybridity' and its importance for evolution [48, 49]. Yet the human nature does not easily accept complexity or the notion of hybridity. New future leaders in science, medicine and society will need to be 'semantic translators', and consider the intersection and interaction of multiple disciplines, generations, cultures and attendant promises and conflicts. Exactly what type of hybridity would be desirable, if public health genomics and personalized medicine will succeed in a sustainable manner?

Khoury

The discussion earlier leads us to the unavoidable conclusion that 21st century medicine and public health sciences will need a "team" integrative approach [50], in which new genomic discoveries are evaluated for their health-related utility from multiple viewpoints and ultimately from the perspective of population health, the ultimate goal of public health genomics. What you call "hybridity" is also referred to as multidisciplinarity and transdisciplinarity [50]. There is an ongoing tension in genomics. One the one hand, bench scientists who are pioneers in gene discoveries and technologies continue to make bold predictions of medical and public health applications and benefits. Nevertheless, these predictions can only be fulfilled if there is ongoing collaboration and involvement of multiple fields of inquiry, especially from the population sciences and the humanities, the domain of public health genomics. The Institute of Medicine's 2006 report on gene-environment interaction stated the need for multidisciplinarity as follows: "Increasingly knowledge is pushing scientists to look beyond single agents of health and disease. By breaking out of their disciplinary "silos" and embracing a broader systems view, based on the understanding that health outcomes are the result of multiple determinants—social, behavioral, and genetic--that work in concert through complex interactions, the best health outcomes from research may be yet to come" [51].

Dubé, Daar and Ozdemir

Could you briefly tell us your vision on public health genomics research and education for the next ten years? Do you have any suggestions for students in both developed and developing countries that aspire for a career in public health genomics and personalized medicine? In particular, when do we start education in the field? Focusing on students at what level, and how do we increase their competency and at what pace? We ask our students to be autonomous and independent but they will need to develop, in parallel, a genuine sense of "global citizenship", well beyond their personal biases, national identities and geographical borders.

Khoury

We truly live in exciting times. At the beginning of my career in genetic epidemiology, I pursued one of these new hybrid fields (genetics and epidemiology) at a time when gene discovery was still rudimentary and the laboratory tools primitive by today's standards. At that time, very few epi-

demiologists pursued inquiries in genetic factors in disease and even fewer examined gene-environment interactions. Geneticists were preoccupied with finding loci for single gene disorders and providing necessary information to patients and families. The passion for making a difference in the health of people was (and still is) a primary driving force. Today, the new generation of scientists and the future scientists will have at their disposal an ever expanding array of tools and technologies that they can apply to their lines of inquiries. However, education must start as early as possible to help shape the inquisitive minds of young people throughout their lifetime. New curricula for education in developed and developing countries will have to include genomics and system biology at all levels as well as a better appreciation of the role of population sciences. At the same time, we need a sophisticated citizenship that appreciates more fully both the future promise and the current limitations of genomic discoveries. At the CDC, we have focused on training and education of the current and future public health workforce as well as dissemination of information to the general public. One of these simple public health messages has been a relatively low tech but important genomic tool, namely family health history [52]. Since 2004, we have collaborated with multiple groups to launch a public health initiative to increase awareness of providers and consumers to the importance of family history in disease prevention and health promotion. I predict family history will remain relevant even after the full complement of genetic discoveries is made. To address the global health challenges, we need to be aware of the promise as well as limitations of genome-based science and technology. Public health genomics provides a multidisciplinary scientific approach to explore and fulfill the promise of this technology and to address and remedy its limitations to benefit the health of citizens of the 21st century.

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DUALITY/CONFLICT OF INTERESTS

None declared/applicable.

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